Oxidative Dearomatization of Naphthols – a Novel Synthesis of Sulphoxide Templates

A Dissertation
Submitted in partial fulfilment

FOR THE DEGREE
OF
MASTER OF SCIENCE IN CHEMISTRY

Under The Academic Autonomy
NATIONAL INSTITUTE OF TECHNOLOGY, ROURKELA

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Certificate

This is to certify that the material presented and performed experiments in this project entitled "Oxidative Dearomatizationof Napthols- a Novel Synthesis of SulphoxideTemplates"is a bonafide record work done by **Sushree Ranjan Sahoo**ofNIT Rourkela, Rourkela in partial fulfilment of requirements for the degree of Master of Science for his research project. He has successfully completed his project work under my guidance in the academic year2013-2014 at the NIT Rourkela.

Date: 06.05.2014 Dr. Debayan Sarkar

NIT Rourkela Project Guide

ACKNOWLEDGEMENT

It is my privilege to epress the feeling of my heart by dedicating this page to people who had been the living inspiration for me for their co-operation and relentless encouragement.

I express my deepest sense of gratitude and indebtedness to **Dr.Debayan Sarkar,**(Asst. Professor, Department of Chemistry, NIT Rourkela)**,**for his ingenious guidance and constructive criticism throughout the period of project work.

I acknowledge the Director and Head of the Chemistry Dept., NIT Rourkela for necessary permission to work and providing departmental infrastructure facilities.

I owe my deep sense of honour and gratitude to my esteemed Manoj Bhai, Nilendri Didi, Sagarika Didi, Rahul and friends for their hearty support and co-operation in various stages of preparation of this project work and project report.

I owe my indebtedness to my beloved parents, brother, sister for their encouragement and inspiration through out the work.

Date: 06.05.2014 Sushree Ranjan Sahoo

NIT Rourkela 412CY2023

DECLARATION

The work ***"Oxidative Dearomatization of Napthols – a Novel Synthesis of Sulphoxide Template"*** embodied in this report and submitted to NIT Rourkela has been carried out by me as a one year Project Fellow during July 2013 – April 2014at NIT Rourkela under the guidance of Dr. Debayan Sarkar . This work is original and has not been submitted for any other degree of this or any other University or Institue.

Date: 06.05.2013 Sushree Ranjan Sahoo

NIT Rourkela 412CY2023

DEDICATED TO MY

BELOVED PARENTS AND LATE

GRAND PARENTS

Contents

Prefatory Notes

All the compounds described and having asymmetric carbons are racemic forms.

Melting Points

Melting points were taken in open capillaries in sulfuric acid bath and are uncorrected.

Infrared Spectra

Infrared spectra were recorded on Shimadzu FTIR-8300spectrometer. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr discs and liquids as thin films in between NaCl plates.

Nuclear magnetic resonance spectra

^{1}H NMR spectra were recorded on Bruker-Avance DPX-400 instrument in $CDCl_3$solutions, unless otherwise stated. Chemical shifts are reported with respect to tetramethylsilane (Me_4Si) as the internal standard (for ^{1}H NMR) and the central line (77.16 ppm) of $CDCl_3$ (for ^{13}C NMR). The chemical shifts are expressed in parts per million (δ) downfield from Me_4Si. The standard abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet respectively. Coupling constant (*J*), whenever discernible, have been reported in Hz.

Mass spectra

Liquid Chromatography with Mass (LCMS) was measured mass spectrometer with an orthogonal Z-spray-electrospray interface on Micro (YA-263) mass spectrometer (Manchester, UK).

Chromatography

Reactions were monitored by thin-layer chromatography (TLC). TLC was performed with silica gel 60 F_{254}aluminium sheets (Merck). Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or using

UV light or by spraying with either ethanolic vanillin solution and heating the plates at 120 ^{o}C.Column chromatography was usually carried out with silica gel (60-120 mesh) and flash chromatography with silica gel (230-400 mesh). The columns were usually eluted with diethyl ether-petroleum ether mixtures and MeOH-ethyl acetate/chloroform solvent systems were used for polar compounds. Petroleum ether refers to the fraction of boiling point 60-80 ^{o}C.

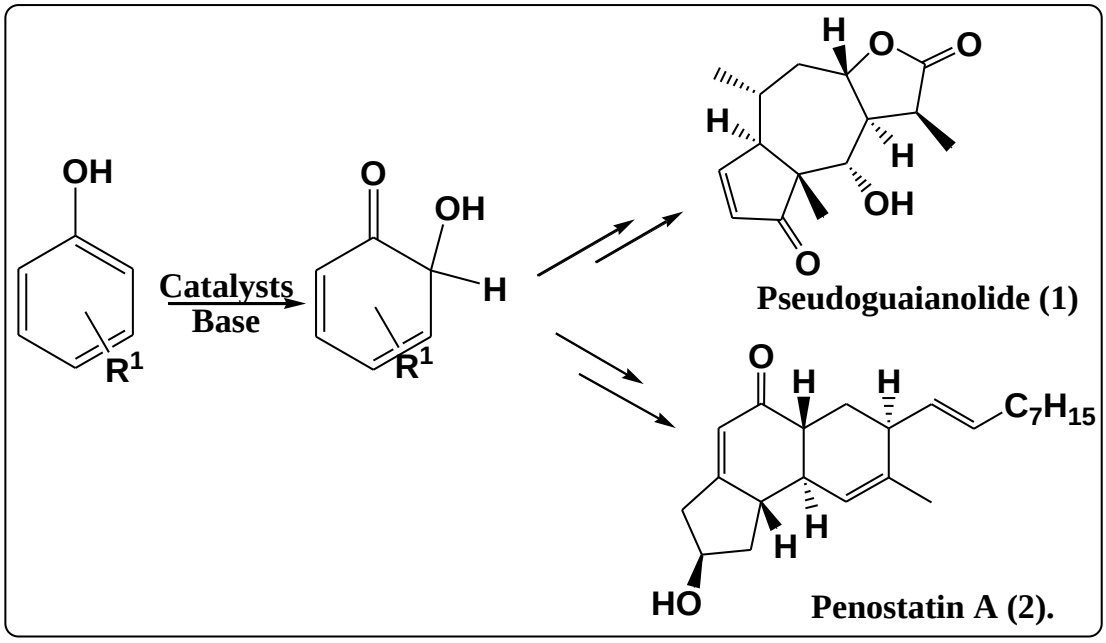
General

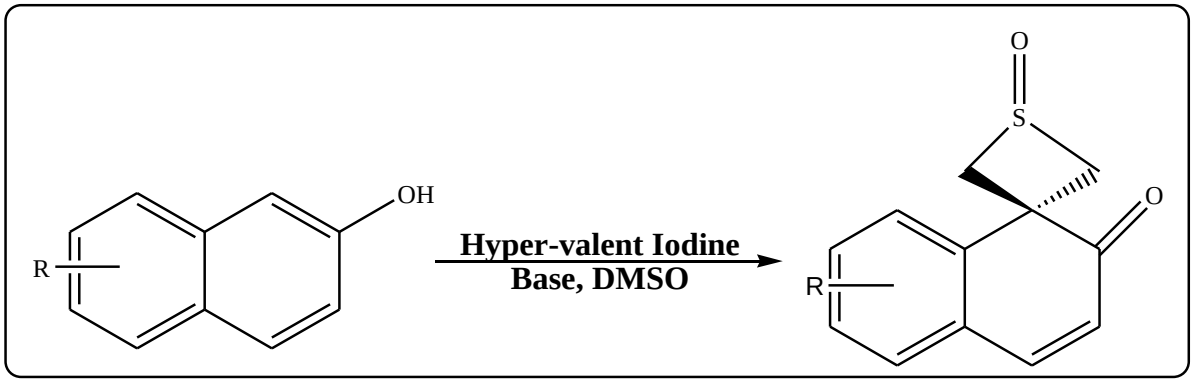
All moisture and air sensitive reactions were performed under argon atmosphere with dry, freshly distilled solvents under anhydrous conditions using standard syringe-septum technique. Tetrahydrofuran (THF), benzene, toluene, dimethoxyethane and diethyl ether were distilled from sodium benzophenoneketyl. DCM, HMPA, DMF and DMSO were distilled freshly from sodium hydride. Allyl bromide was distilled over calcium chloride. Vinyl bromide was freshly prepared and distilled over calcium chloride prior to use. Acetone was distilled over potassium carbonate. MeOH was distilled from its alkoxide (formed by the reaction with activated magnesium) and stored over 4Å molecular sieves. ^{t}Butanol was dried over sodium and freshly used. Pyridine and triethyl amine were distilled over potassium hydroxide pellets and stored over the same.

A usual workup of the reaction mixture consists of extraction with ether, washing with water, brine, drying over Na_2SO_4, and then concentrated under reduced pressure on a rotary evaporator unless specified. Yields reported are isolated yield of material judged by homogeneous TLC and NMR.

Abstract:

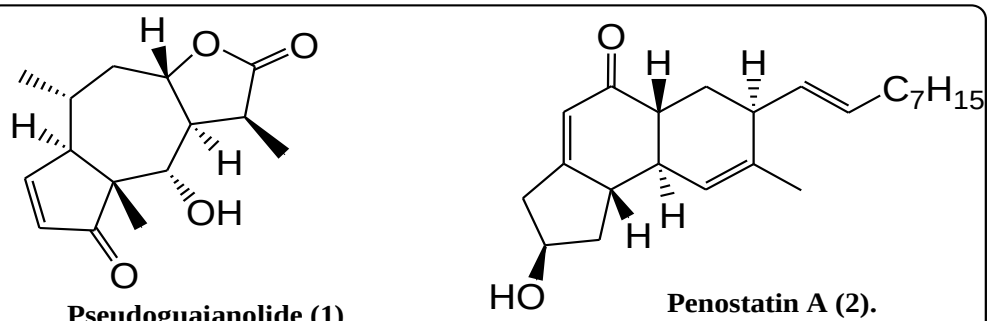
Development of facile routes to accomplish successful multistep organic synthesis, leading to the development of bioactive natural products is one of the most challenging fields in chemistry in academic and industry throughout the world. Our interest lies in Oxidative Dearomatization of unprotected systems like phenol, cresols, coumarins, napthols etc. using hyper-valent Iodine catalysts which can lead to versatile frameworks for active organic practioners. Intial approaches towards two Bioactive Natural Products namely Pseudoguaianolide (1) and Penostatin A (2) lead us to explore newer methodologies for scalable Oxidative Dearomatization. In an event of experiments leading to this methodology, a novel transformation leading to formation of sulphoxide templates have been brought under the preview of this project and elaborated in the following pages.





1. Introduction:

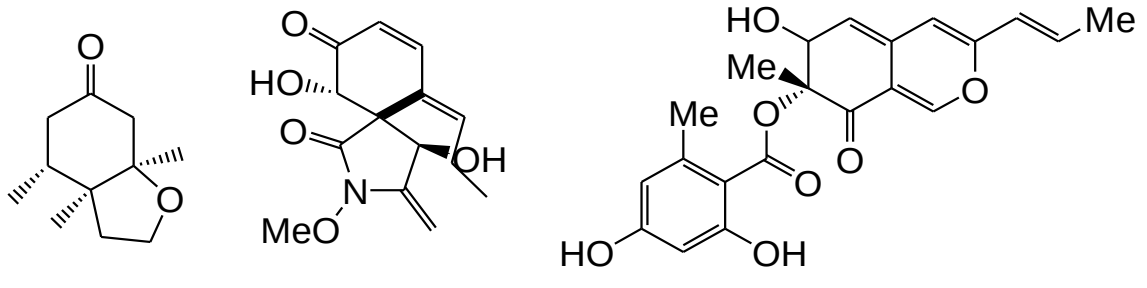
The main objective of the project was to develop better synthetic approach to tricyclic ring systems present in two different natural product namely as *Pseudoguaianolide**(1)*** and *Penostatin A**(2)*** as shown in figure-1.



Pseudoguaianolide (1) **Penostatin A (2).**

Figure-1

*Pseudoguaianolide**(1)*** has a linear tricyclic frame work whereas, in *Penostatin A**(2)*** both linearly and angular fusion of ring systems are observed, which makes them and interesting target to organic chemists. Not only the structural integrity but also the bioactivity of the natural product is of great concern. Both of natural products exhibit fantastic antibiotic properties.[1] Retrosynthetically we envisaged that, total syntheses of both these natural products could be approached from a suitably substituted Hydroxy-indanone and substituted coumarin *via* a common *Oxidative -Dearomatization* strategy. Not only this, but Oxidative Dearomatization has been a common protocol in developing huge class of natural product through years[2] as shown in figure-2.



(+)- Cleroindicin D **Spirostaphylotrichin A** **(-)-Mitorubrin**

Figure-2

1.1 Synthetic Methodology:

The oxidation of aromatics has been one of the interesting areas of synthetic importance. The oxidative transformation of phenol leads to cyclohexadienones, oxidative coupling, ortho-hydroxylation and ring cleavage reactions. Specifically, the cyclohexadienone is expected to deliver suitable scaffolds for different interesting transformations as shown in figure-3.

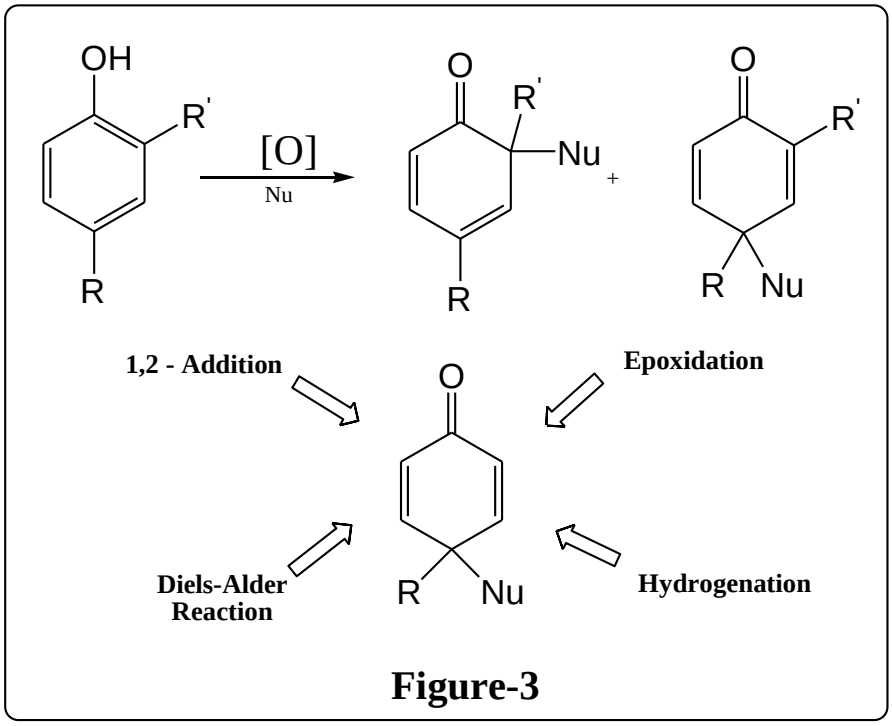


Figure-3

Oxidative Dearomatization serves to be a simple strategy for the generation of chiral centres in one step, though breaking of aromaticity at the basic step doesn't seen to be easy. Oxidative Dearomatization has been nucleophilic or, electrophilic in nature[3] as shown in figure-4.

The basic step has been expected to go through a simultaneous nucleophilic addition to a cyclohexadienone intermediate. The driving force of the reaction is depends on the activating reagents, structural feasibility and cascade reaction sequence[4] as shown in figure-5.

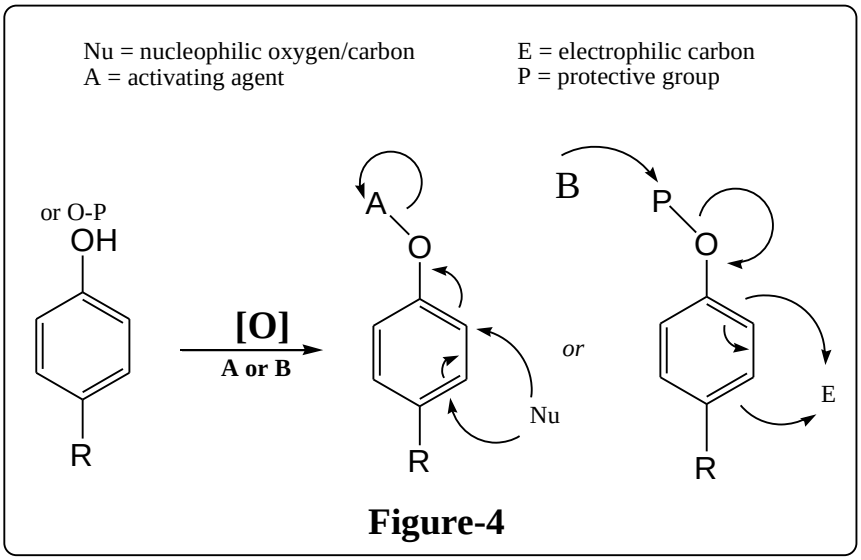


Figure-4

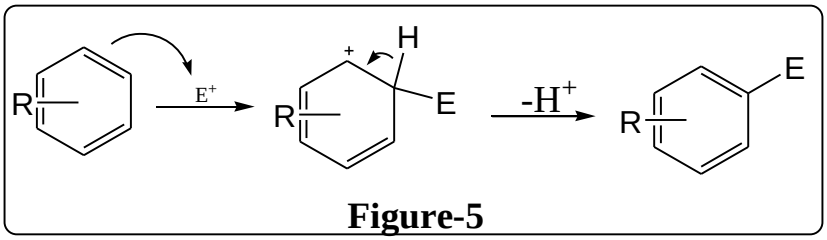


Figure-5

Till today, synthetic protocols towards Dearomatization reaction have been carried out using – A. enzymatic path way

B. thermal or photochemical
C. transition metal catalysed
D. hyper-valent Iodine,
E. Birch reduction or hydrogenation as shown in figure-6.

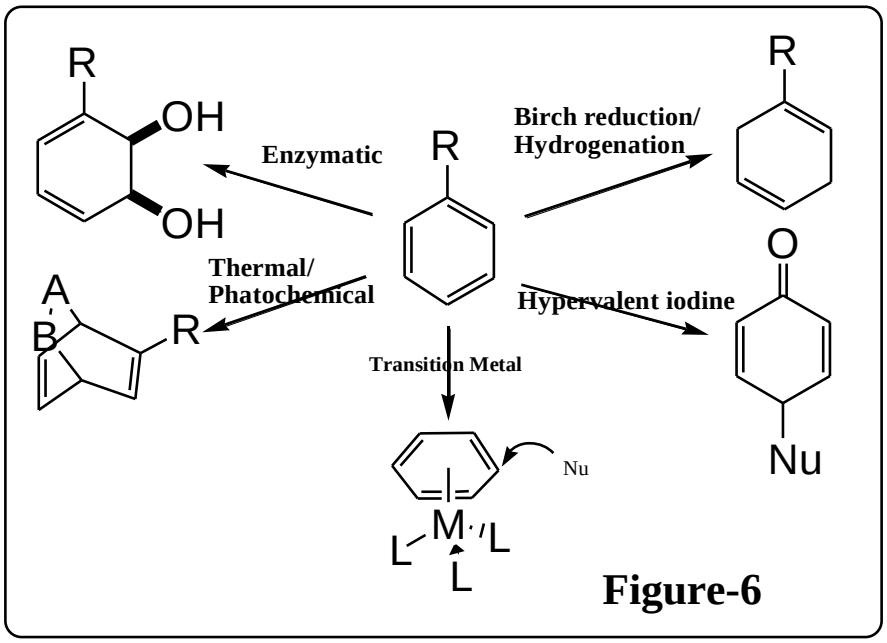


Figure-6

However use of trivalent iodine in reagent like PIDA (bis (acetoxy) iodobenzene) to the maximum extent. Hyper-valent Iodine like I^{+5}have not been explored to that extent, neither different substituted trivalent Iodine has been explored for Oxidative Dearomatization. The cyclohexadienone intermediates which solve out in the Oxidative Dearomatization reaction has been a key intermediate for tandem [4+2] cycloaddition reaction[5], triggering intermolecular Diels-Alder reaction[6], Michael addition[7], Claisen dearomatization[8] etc. Our attraction towards developing a convent synthetic tool for such cyclohehadienone and exploring the possibility of employing I^{+5}catalysts has been the main area of this project as shown in figure-7.

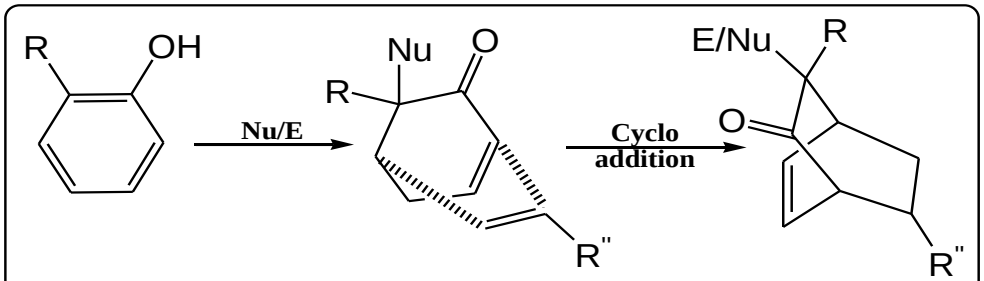


Figure-7

1.2 Earlier Work with I^{+3} Reagents:

Liao et.al.Develop a short synthesis of tricyclic natural product *Penicillone B* employing PIDA mediate Oxidative Dearomatization as a key step[9] as shown in figure-8.

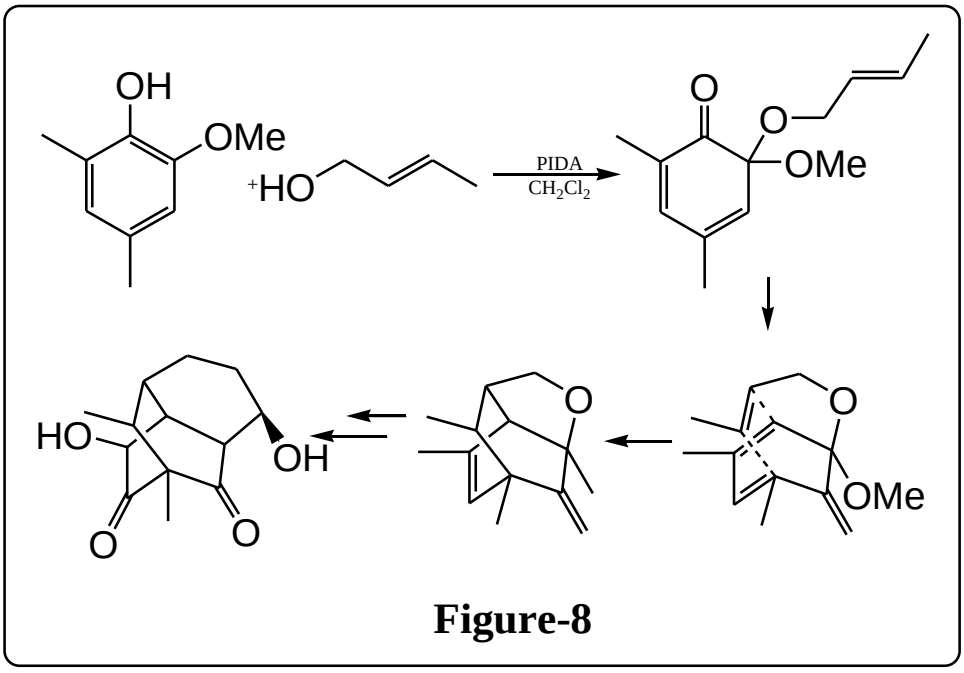


Figure-8

Use of I^{+3}reagents for enantioselective Oxidative Dearomatization has been recent area of renound organic chemist throughout the world. Recently, Nicolau et.al. Reported a total synthesis of the renound molecule *(-)-Platensimycine* where the Oxidative Dearomatization using the same I^{+3} catalysts [10] as shown in figure-9.

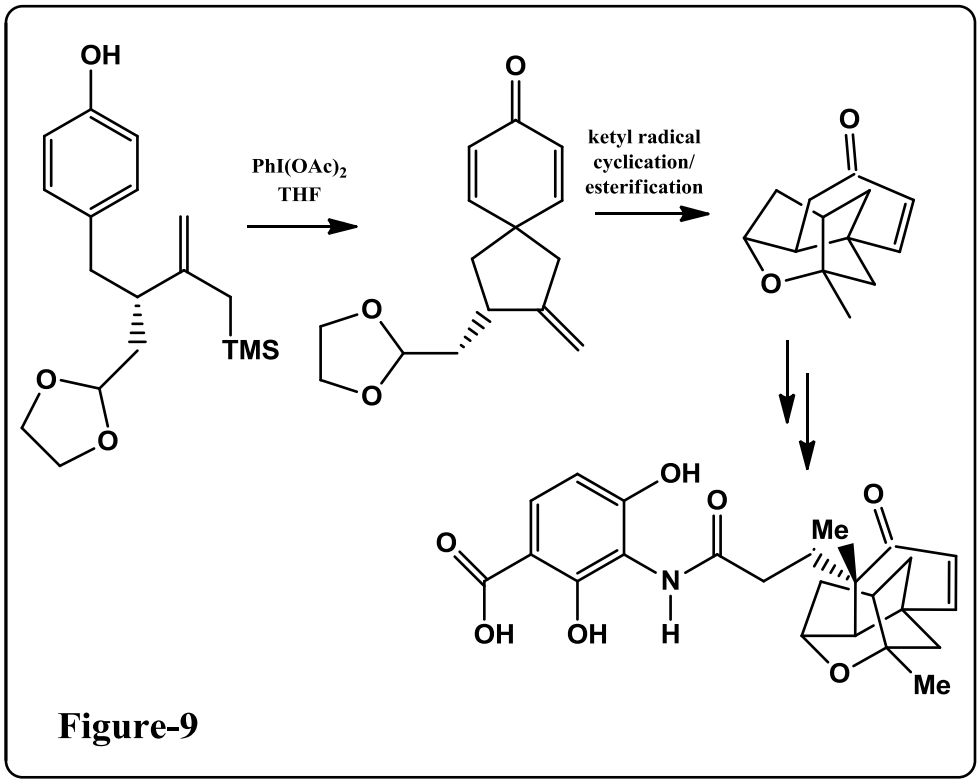


Figure-9

1.3 Introduction to Sulphoxides:

The past two decades have been seen an explosion in interest on synthesis and utility of molecule containing stereo-genic sulphur centre[11] an important subclass of this classes of this sulphoxides. Through this structural motive typically represent in Lewis structures as analogous to a carbonyl moiety, the sulphur atom of the sulphoxide is in fact a stereo-genic centres when R1≠R2 as shown in figure 10.

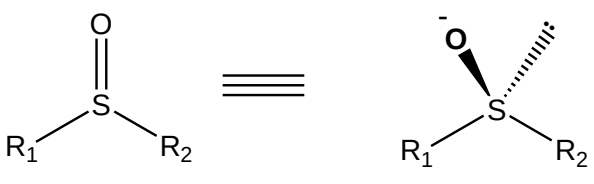


Figure-10

The oxygen and sulphur do not share a typical p-orbital pi bond which would enforce a planar conformation, but rather the oxygen donates electron densityfrom a lone pair into a d-orbital of sulphur. This d-π bonding allows the sulphur to assume tetrahedral sp3 hybridization, with a lone pair of electrons from sulphur as "placeholders" in the fourth quadrant. Sulphoxides are conformationally stable at room temperature. Sulphoxides are found in a variety of natural products. They have also been employed as chiral auxiliaries in a range of reaction classes, and more recently as chiral ligands. Sulphur is well-suited to therole of an agent for transfer of chirality for several reasons. The application of chiral sulphoxides as ligands for transition-metals has been less thoroughly explored to date than their use as chiralauxiliaries. Recently, Dorta reported the first highly enantioselective reaction using a bis-sulphoxide ligand.[12] Therhodium/bis-sulphoxide catalyzed conjugate addition of aryl boronic acids to α,β-unsaturated ketones proceeded in excellent yields and enantioselectivities as shown in figure-11.

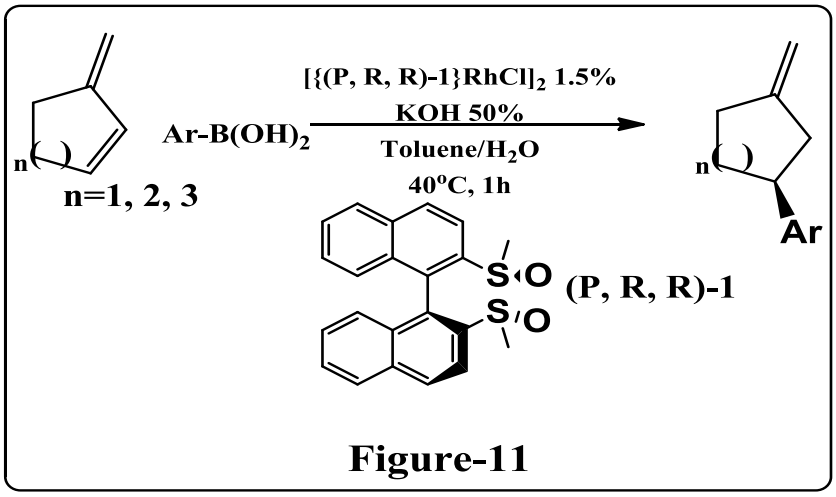
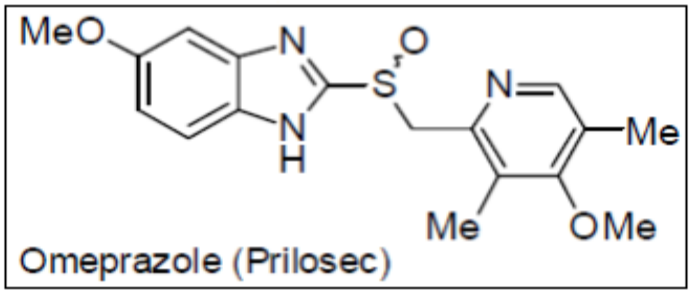
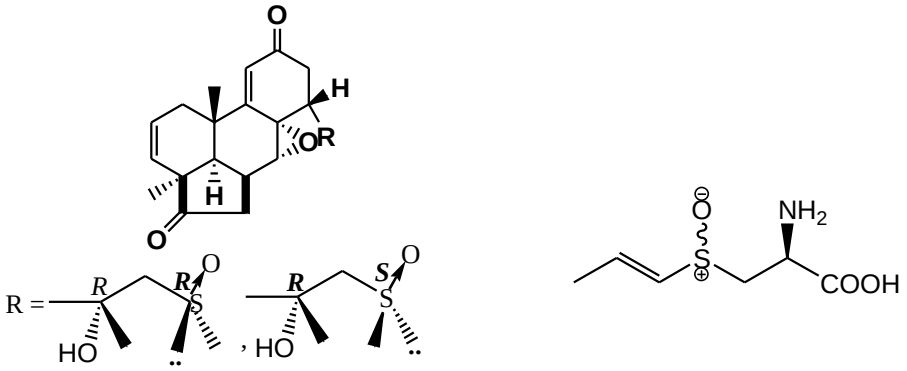


Figure-11

Not only have the chiral auxiliary sulphoxides been an integral part for important drugs ***Omeprazole***, which is being widely used as a drug for inhibition of gastric acid secretion. Sulphoxides also have been found of huge class of natural products like ***Cysteine Sulphoxid*** [13] and ***Podolactone D***[14] as shown in figure- 12.





Podolactone D **Cysteine Sulfoxide**

Figure-12

The most straight forward route to enantiomerically enriched sulphoxides involves preparation and substitution of a pure diastereomer using a chiral reagent. Following pioneering work by Gilman on theattack by Grignard reagents on sulphonic esters,[15] Andersen reported the first practical synthesis of chiral sulphoxides in 1962[16] as shown in figure-13.

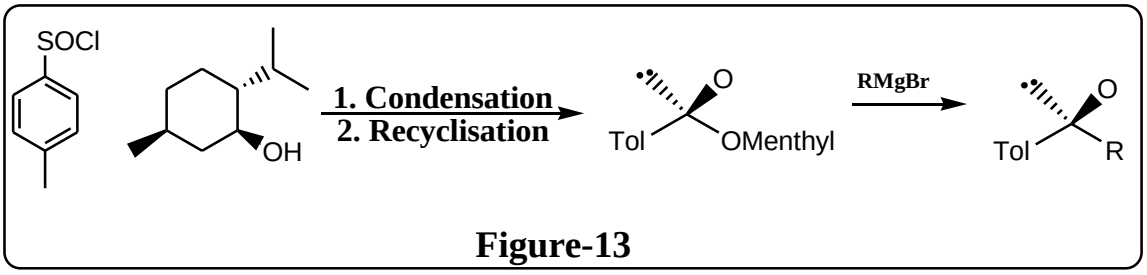


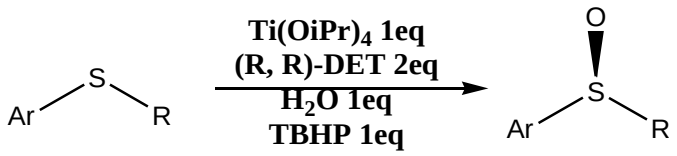
Figure-13

Condensation of toluene sulphinyl chloride with optically pure (-) -menthol yields a mixture of diastereomers which can be separated by recrystallization. Nucleophilic attack by an organo-magnesium halide reagent displaces mentholate with clean inversion at the sulphur center. Though this is still a widely used method, it suffers from limitations. The menthol sulphinate-ester can only be recrystallized efficiently if it bears an aryl substituent, so dialkylsulphoxides are not accessible by this method. Second, the initial condensation proceeds without diastereoselectivity. Though Solladie and coworkers have developed an epimerization equilibration method to improve the yield of the desired diastereomer,[17] repeated recrystallizations are often necessary.

1.4 Synthetic Strategy for Sulphoxides:

Developing a common protocol for poly functionalised sulphoxides as a remain challenged to organic chemist, because of their huge application. Some of the common strategy involves catalytic oxidation of sulphoxides.[18] However developing of chiral sulphoxides have been reported by Kagon and Sharpless.[19]Both involve modifications to Sharpless' titanium catalyzed asymmetric epoxidation reaction. Kagan and coworkers discovered that addition of stoichiometric water to the catalyst was crucial to achieve enantioselectivity in the oxidation of sulphides. Yields and enantioselectivities were high for aryl alkyl sulphoxides and moderate for dialkylsulphoxides as shown in Table -1.

Table-1



Entry	Ar	R	Yield (%)	e.e. (%)
1	p-$CH_3C_6H_4$	Me	90	90
2	p-$CH3O_2CC_6H_4$	Me	50	91
3	p-$CH3OC_6H_4$	Me	72	86
4	p-$CH_3C_6H_4$	Et	71	74
5	p-$CH_3C_6H_4$	i-Pr	56	63
6	$(CH_3)_3C$	Me	72	53

But all of them required highly expensive transition metal catalyst. However, the synthetic approach has been used to prepare a simple cyclic sulphoxides. So designing of a one pot strategy for creating stable sulphoxide templates are worthy target for organic chemist. As the stable sulphoxide template can be verity of new transformation leading to important discoveries.

2. Present Work:

The present project was focused initially on developing of new derivatives of hyper-valent I^{+3} and I^{+5}. For example shown in figure-14.

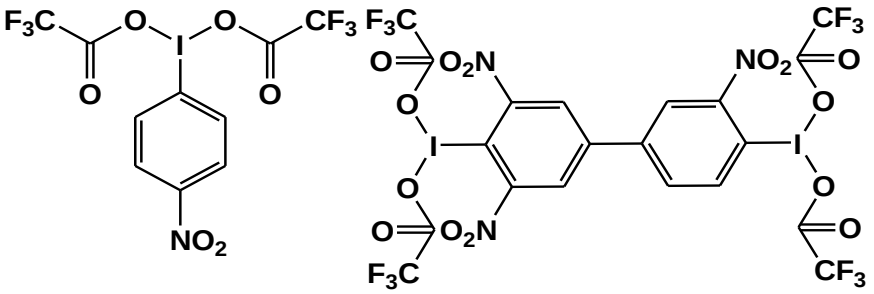


Figure-14

A number of substrates like phenols, hydroxyl coumarins, napthols, heterocyclic e.g. 3-hydroxy pyridine where exposed to Oxidative Dearomatization condition in presence of a suitable base, it exhibit the presence of equilibrium (more specially *keto-enol* tautomerism) with multiple peaks in crude NMR, when the NMR just after the reaction. It was reviled that quenching of the reaction mixture fully delivered the starting material as a whole. Presence of the equilibrium was conformed, when repeated experiment were carried out in a verity of substrates, different bases, with different oxidants and different thermal & photochemical condition. But in all cases, the starting substrate was isolated when the reaction mixture was quenched.

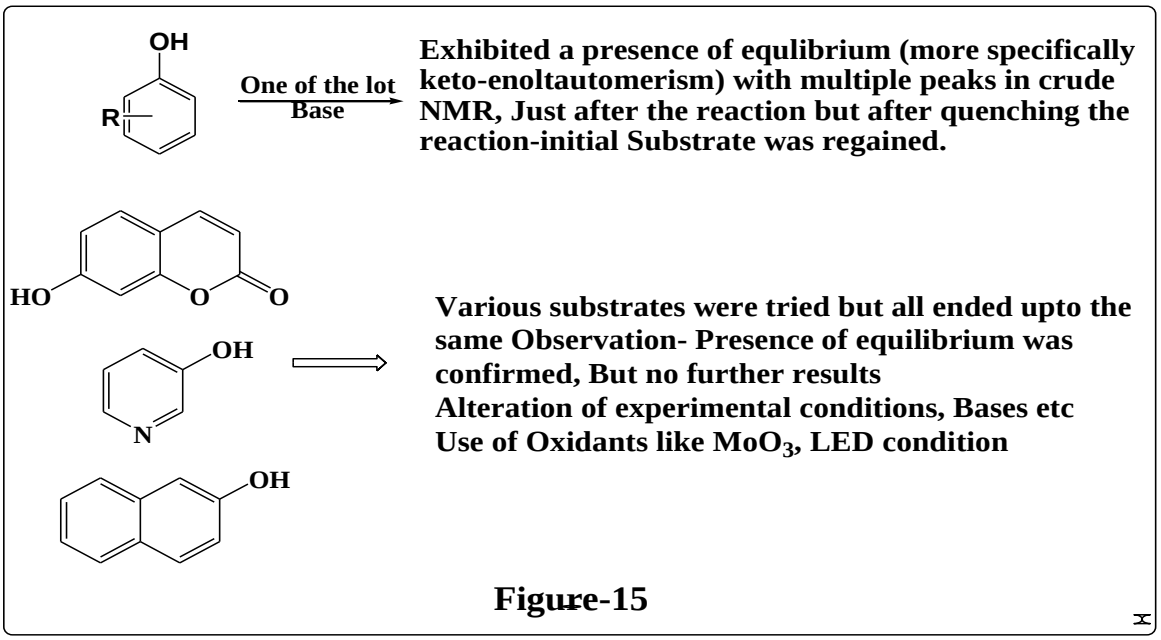


Figure-15

In an event, while reacting β-napthol with one of hyper-valent Iodine in a suitable base in DMSO, an interesting spiro-sulphur was isolated. Reaction has been carried out both α- & β-napthols and the reaction proceeds in a good yield in both the substrates and resulting into spiro-sulphones. However, serious NMR study reviles the presence of ***Sulphoxide-A*** (from β-napthol).The ^{13}C-NMR spectrum reviles the peaks found to be expertly doubled. Whereas no such observation were found in case of the ***Sulphoxide-B*** (from α-napthol) as shown in figure-16.

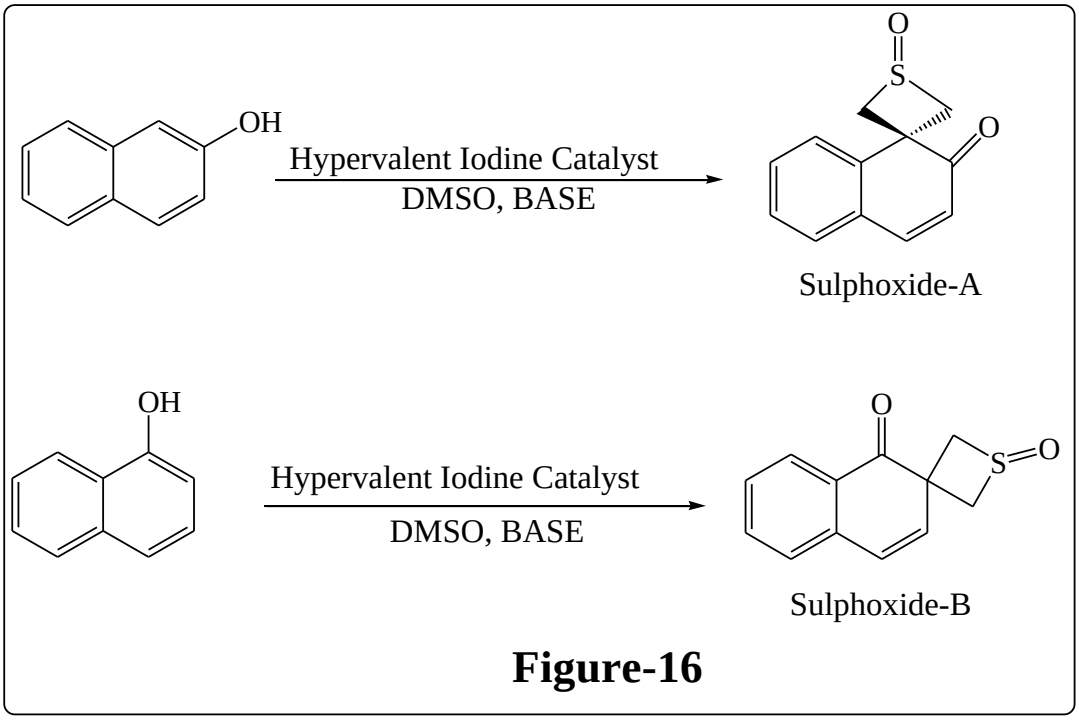
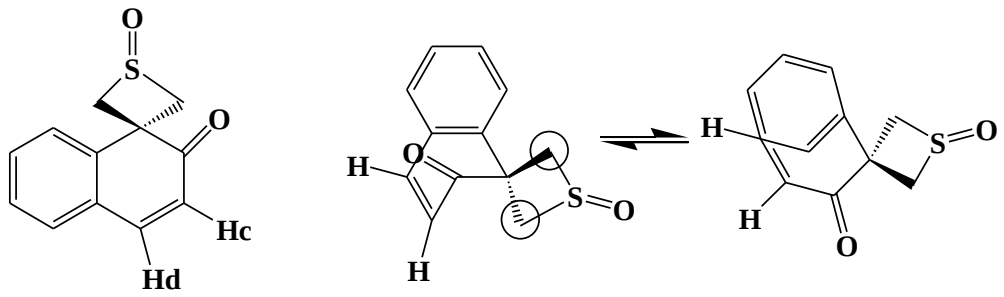


Figure-16

No peri-hydrogen effect also was encounted in the ^{1}H-NMR of Sulphoxide-B further conform the structure. However, the presence of two methylene group in Sulphoxide-A compare to Sulphoxide-B, Further confirms the fact that the continuous flipping of the spiro-sulphoxide is responsible for the presence of extra peaks in ^{1}H-NMR spectrum of sulphoxide-A. Presence of four member sulphoxide in the 2-position in between the benzylic carbonyl and the alkenes, which restricts the flipping of the cyclohexenone ring in Sulphoxide-B as compare to Sulphoxide-A as shown in figure-17.

For Sulphone-A:



For Sulphone-B:

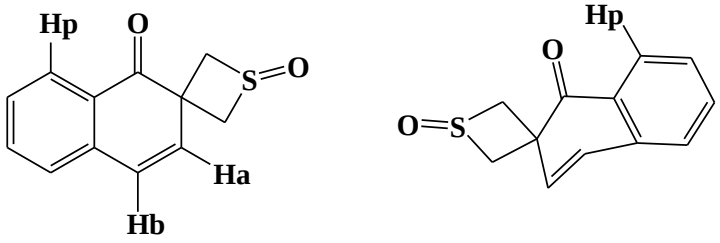
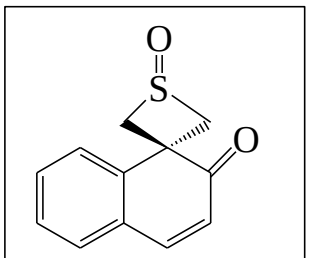


Figure-17

3. Experimental:



Sulphoxide-A

Molecular Formula: $C_{12}H_{10}O_2S$

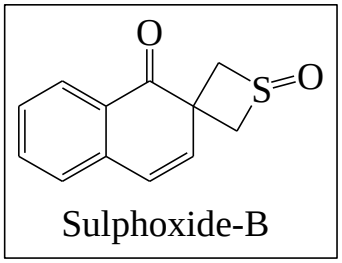
Molecular Weight: 218.27

Nature: yellow thick liquid

Mass Spectra: 219.27 $[M^+ + 1]^+$

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.48(s, 3H), 4.14(s,3H), 4.30-4.34(m, 2H), 4.35(t, *J=6.4Hz* ,2H), 7.77(dd, *J=1.2Hz*, 1H), 7.66(ddd, *J=1.2Hz*, 1H), 7.74-7.79(m, 3H), 7.94-7.97(m, 2H), 8.23(dd, *J=1.2 Hz*, 1H) ppm.

^{13}C NMR ($CDCl_3$, 400 MHz): δ = 168.07, 167.40, 143.27, 133.53, 131.92, 131.46, 131.13, 130.92, 130.19, 129.84, 129.34, 128.89, 128.85, 127.17, 52.67, 51.81, 30.94, 30.56, 29.70, 29.37 ppm



Sulphoxide-B

Molecular Formula: $C_{12}H_{10}O_2S$

Molecular Weight: 218.27

Nature: yellow thick liquid

Mass Spectra: 219.27 $[M^+ + 1]^+$

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.24(s, 3H), 0.06(s, 3H), 7.04(77, *J=0.8, 1.2 Hz*, 1H), 7.49-7.79(m, 4H), 8.03(dd, *J=2.8, 2.4 Hz*, 1H), 8.49(dd, *J=2.8, 2.4 Hz*, 1H) ppm.

^{13}C NMR ($CDCl_3$, 400 MHz): δ = 155.42, 134.46, 127.42, 126.36, 125.82, 125.59, 125.14, 121.96, 120.21, 103.72, 55.46, 31.95 ppm

4. Conclusion:

A facile one port synthetic strategy has been developed from napthols using hyper-valent iodine catalysts in DMSO solvent. Further study of low temperature NMR is under progress.

5. References:

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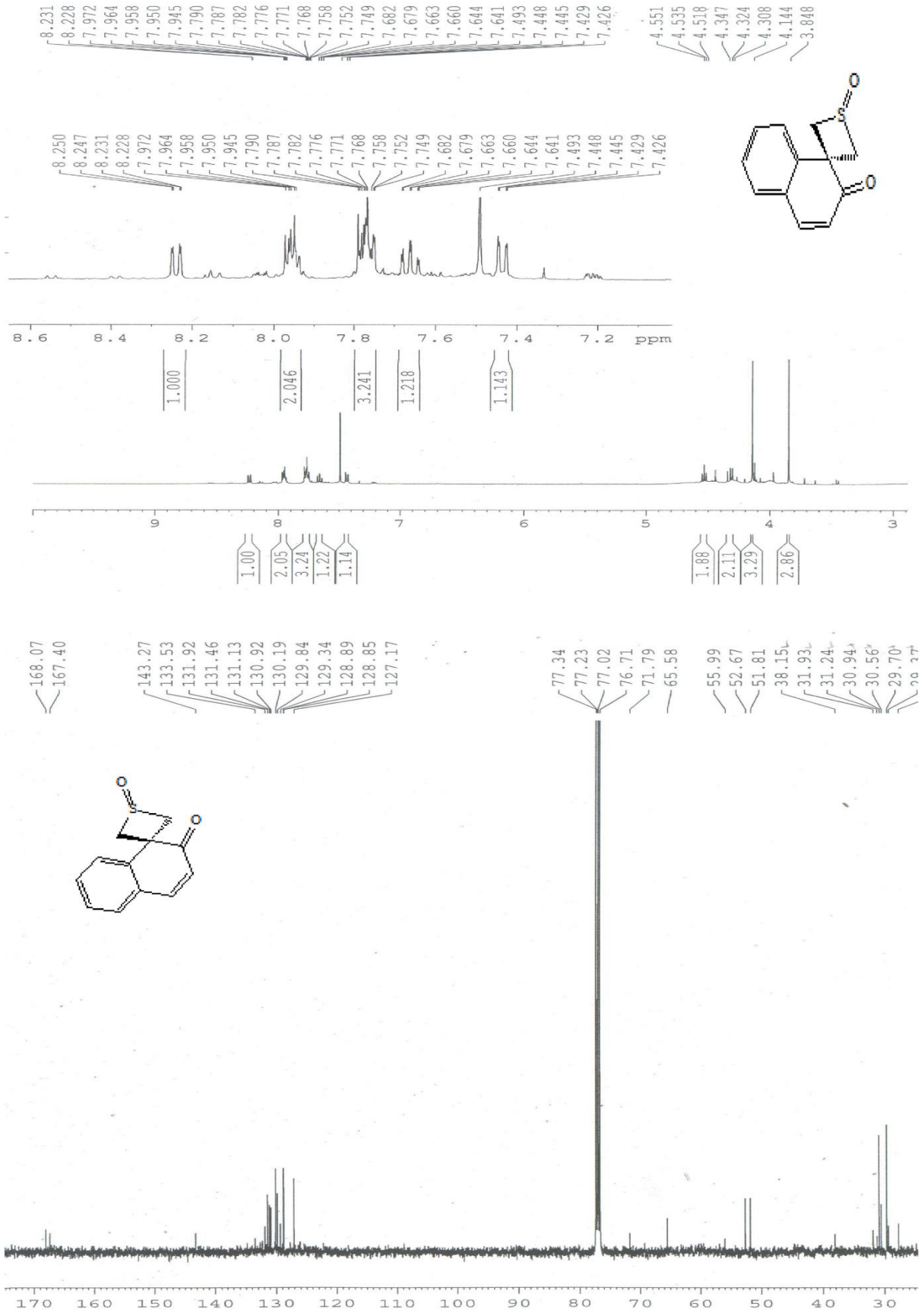
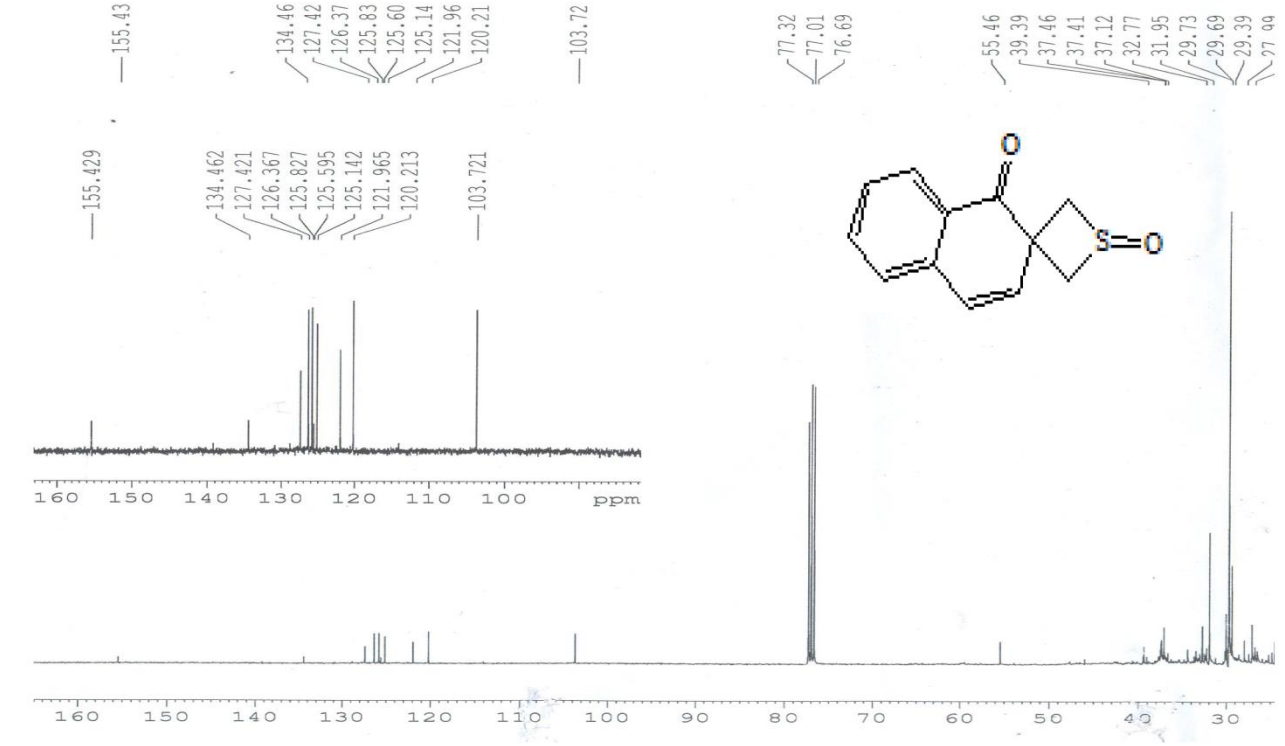
6. Spectral Data:




8.513
8.505
8.495
8.489
8.046
8.040
8.031
8.022
7.742
7.730
7.725
7.722
7.714
7.705
7.702
7.697
7.685
7.675
7.655
7.637
7.619
7.598
7.492
7.064
7.061
7.045
7.043
4.900
4.243
O
S=O
ppm
1.000
1.064
1.941
0.466
1.870
1.022
1.00
1.06
1.94
0.47
1.87
1.02
3.27


155.43
134.46
127.42
126.37
125.83
125.60
125.14
121.96
120.21
103.72
77.32
77.01
76.69
55.46
39.39
37.46
37.41
37.12
32.77
31.95
29.73
29.69
29.39
155.429
134.462
127.421
126.367
125.827
125.595
125.142
121.965
120.213
103.721
O
S=O
ppm